CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-385

APPROVAL LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-385

Mylan Pharmaceuticals, Inc.
Attention: Andrea B. Miller, R.Ph., Esq.
Executive Director, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

Dear Ms. Miller:

Please refer to your new drug application (NDA) dated September 28, 2001, received September 28, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ERTACZO™ (sertaconazole nitrate) Cream, 2%.

Please also refer to your October 9, 2003, response to our July 26, 2002, action letter.

We acknowledge receipt of your submissions dated October 24, December 2, 5, 8 and 9 (facsimiles), 2003.

The October 9, 2003, submission constituted a complete response to our July 26, 2002, action letter.

This new drug application provides for the use of ERTACZO™ (sertaconazole nitrate) Cream, 2%, for the topical treatment of interdigital tinea pedis in immunocompetent patients 12 years of age and older, caused by *Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum.*

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We remind you of your postmarketing study commitment in your submission dated December 5, 2003 (facsimile). This commitment is listed below.

Commitment/Study Description: Conduct a dermal carcinogenicity study.

Commitment Category: Non-Clinical Toxicology:

Protocol Submission:	by March 10, 2004.
Study start:	by December 10, 2004
Final report submission:	by December 10, 2007

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

With regards to the pharmacokinetic data, for this and future NDA's, we encourage you to conduct future *in vivo* bioavailability trials under maximum use conditions in patients with the desired indication. In general, such studies should enroll a sufficient number of subjects (generally >15) to assure the proper characterization of circulating drug levels where feasible. The use of pooled data from mixed indications, although allowed in the past, does not represent current thinking in this area.

For this and future NDAs, we ask that any future clinical studies be designed to establish a correlation between clinical and microbiological outcomes. These studies should include *in vitro* susceptibility evaluations of the relevant fungal pathogens isolated from a sufficient number of patients enrolled. The *in vitro* susceptibility studies must demonstrate the fungicidal activity of the test drug against all relevant pathogens for the requested indications. While data from animal models may help evaluate the equivalent human clinical dose, and pre-clinical *in vitro* susceptibility results may demonstrate the spectrum of activity of the test drug against selected fungal strains, the *in vitro* susceptibility to the test drug of the causative pathogens isolated from the target site in patients enrolled in clinical trials helps confirm microbiological and clinical efficacy.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonca Bull, M.D.
Office Director
Office of Drug Evaluation V

Enclosure

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APPLICATION NUMBER:

21-385

APPROVABLE LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-385

Mylan Pharmaceuticals, Inc.
Attention: Frank Sisto, Executive Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

Dear Mr. Sisto:

Please refer to your new drug application (NDA) dated September 28, 2001, received September 28, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ERTACZO™ (sertaconazole nitrate) Cream, 2%.

We acknowledge receipt of your submissions dated November 15 and 21, 2001, and January 4 and 21, February 5, March 1 and 7 (2), April 5, 19 and 24, May 16 and 22, 2002.

We also acknowledge receipt of your submissions dated July 10 and 16, 2002. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

This new drug application provides for the use of ERTACZO™ (sertaconazole nitrate) Cream, 2%, for

We have completed our review of this application, as submitted, for the — ontaining formulation of ERTACZO™ Cream, 2% and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following:

1.

2. Revised draft labeling for the drug as indicated in the enclosed draft labeling.

In addition, the following studies would provide useful information in labeling for the safe and effective use of ERTACZO™ Cream 2%. Some of these may be able to be conducted in the course of further development prior to approval. If you do not complete these studies prior to approval, they would likely constitute requests for postmarketing commitments.

Pharmacology/Toxicology:

A dermal carcinogenicity study is needed.

This requirement derives from the proposed indication, in which chronic repeated use is anticipated. (ICH S1A, "For pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed.")

Biopharmaceutics:

The major pharmacokinetic study for this application is inadequate for the assessment of in vivo bioavailability.

Clinical Microbiology:

Other Recommendations:

Please note that if you amend this application, the cover letter should unambiguously identify the proposed to-be-marketed formulation (i.e. — containing or — free).

While not approvability issues for the — containing formulation, the following issues have been identified and, if you choose the — free formulation, should be addressed in future submissions for the — free formulation of ERTACZO™ Cream, 2%.

Chemistry, Manufacturing and Controls:

1. The drug substance specification contains a [redacted] which does not conform to the recommendation in ICH Q3A, Impurities in New Drug Substances.

   Since [redacted] impurities above the identification threshold of 0.1% (assuming a maximum daily dose of 100 mg of sertaconazole nitrate) have been identified as [redacted] he specification should be revised to specify these impurities individually, as well as to include an acceptance criterion of [redacted] for any unspecified impurity.

2. The drug product regulatory and stability specifications contain a [redacted] which does not conform to the recommendation in ICH Q3B, Impurities in New Drug Products. Since [redacted] impurities above the identification threshold of 0.2% (assuming a maximum daily dose of 100 mg of sertaconazole nitrate) have been identified as [redacted] he specification should be revised to specify these impurities individually, as well as to include an acceptance criterion of [redacted] for any unspecified impurity. The recommended section is shown here:

Test	Acceptance Criterion	Procedure
[redacted]		
Impurity [redacted]	NMT [redacted]	
Impurity [redacted]	NMT [redacted]	
Impurity [redacted]	NMT [redacted]	
Any Individual Unspecified Impurity	NMT [redacted]	
Total	NMT [redacted]	

* To be determined upon further review of data.

3. The "Description" test acceptance criterion for drug product is listed as [redacted] This should be revised to declare the actual observation, i.e., [redacted] This is required to allow detection of changes during storage. The corresponding method [redacted] should be revised accordingly.

4. The "Identification" test acceptance criterion for drug product is listed as [redacted] This should be revised to declare the actual observation, i.e., [redacted] This is necessary to allow detection of changes during storage. The corresponding method [redacted] should be revised accordingly.

5. Updated stability data for the drug product's primary stability lots submitted in the NDA should be provided. The data from the stability studies performed at [redacted] which reportedly showed incompatibility of the drug product with these conditions, should be provided to justify your decision to study the drug product only under the intermediate conditions.

6. The protocol for selection of units of the finished drug product for release testing should be described in the master batch record.

7. The UV-Visible absorption spectrum of sertaconazole nitrate drug substance should be submitted for reference.

8. A revised master batch manufacturing procedure, deleting the [redacted] from the formulation is needed.

9. A revised finished drug product specification, which omits the [redacted] is needed.

10. Revisions to the carton, container, and package insert labeling to remove the reference to [redacted] in the list of ingredients should be addressed in the revised draft labeling.

11. Revised qualitative and quantitative statements of composition are needed.

12. A revision to indicate that the supporting stability data submitted in the NDA would be considered as the primary data, and the data derived from [redacted] containing lots would be considered supporting lots.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - [redacted], provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on the information submitted in this application, we conclude the following:

For the [redacted] ve note that you will have fulfilled the pediatric study requirement for this application for interdigital tinea pedis for pediatric patients 12 to 18 years of age. We are waiving the pediatric study requirement for this application for pediatric patients less than 12 years of age on the basis that interdigital tinea pedis is not widely seen in this population.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment or follow one of your other options under 21 CFR 314.110.

If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Dermatologic and Dental Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonca Bull, M.D.
Office Director
Office of Drug Evaluation V

Enclosure

35 Draft Labeling Page(s) Withheld

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonca Bull
7/26/02 04:07:35 PM